TABLE III.—CARCINOMATOUS ULCERS.

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypoacidity.	Per cent.	Normal.	Per cent.	Hyperacidity.	Per cent.	No test meal.	Per cent.
Not located	22	27.50	6	27.27	3	13.63	5	22.72	7	31.36	1	4.54
Inoperable	..	.....	..	.....	..	.....	..	.....	..	.....	..	
Pyloric .	50	62.5	10	20.00	..	12.00	22	44.00	12	24.00	..	
Middle .	3	3.75	1	33.33	..	.....	2	66.66	..	.....	..	
Cardia .	5	6.25	1	20.00	..	.....	1	20.00	..	.....	3	60.00
Ignoring location	80	.....	18	22.50	9	11.25	30	37.5	19	23.75	4	5.00

TABLE IV.—CARCINOMA AND CARCINOMATOUS ULCERS.

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypoacidity.	Per cent.	Normal.	Per cent.	Hyperacidity.	Per cent.	No test meal.	Per cent.
Not located	144	22.82	73	50.69	15	10.41	27	18.75	11	7.63	18	12.5
Inoperable	66	10.45	40	60.6	8	12.12	11	16.66	4	6.06	3	4.54
Pyloric .	347	54.99	104	47.26	59	17.0	76	21.9	27	7.78	21	6.05
Middle .	30	4.75	12	40.0	11	36.66	7	23.33	..	.....	..	
Cardia .	44	6.97	25	56.81	3	6.81	5	11.36	2	4.5	9	20.45
Ignoring location.	631	.....	314	49.76	96	15.21	126	19.96	44	6.97	51	8.08

acid values represent the highest reading obtained by a fractional analysis of the gastric contents; this, I believe, gives a greater chance of obtaining higher and more accurate values than the single tubing.

THE RELATION OF ACROMEGALY TO THYROID DISEASE: WITH A STATISTICAL STUDY.*

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AND

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The view that acromegaly is caused by hyperactivity of the anterior pituitary body after epiphyseal union has taken place is generally accepted. Cushing,[1] however, adduced experimental evidence to show that the disease is due to some perversion of secretion rather than merely to an excess of normal secretion.

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With the slow and gradual development of the affection the sella turcica dilates into a cavity of variable size, as shown by a roentgen-ray examination. In practically all cases of acromegaly that have come to autopsy enlargement or disease of the hypophysis has been found, with a corresponding dilatation of the sella turcica and persistence of the thymus in most instances. The new growths of the pituitary gland may be of different character, *e. g.*, adenoma, sarcoma, carcinoma and cystic degeneration. It is generally held that the majority are adenomata. Sternberg[2] states that the acute form of acromegaly is due to a rapidly progressive tumor, frequently sarcoma, of the hypophysis. The enlargement may be due to functional hypertrophy with or without hyperplasia of the chromophile cells.

On the other hand it has been shown that destructive lesions of this gland may be at times unaccompanied by clinical symptoms of acromegaly.[3] In 1891 one of us (Anders) and Henry W. Cattell reported to the Philadelphia Neurological Society a hemorrhagic tumor of the pituitary body and infundibulum which had been unattended with any signs of acromegaly during life.

Conversely, Arnold and Ponfick[4] have reported cases of acromegaly with the pituitary glands normal in all respects. It is true, as pointed out by Friedman,[5] that all ductless-gland disturbances may manifest themselves clinically without gross or microscopical changes. Hemmeter[6] has also emphasized the occurrence of endocrine syndromes without actual pathological alterations. These are termed "ductless-gland neuroses." Among predisposing factors in acromegaly, the role of some of which are still in doubt, are race, age, sex, heredity and trauma, to which detailed reference will be made hereafter.

In 1886 Rogowitsch,[7] and later Stieda[8] and Hofmeister,[9] noted hypertrophy of the pituitary after removal of the thyroid in rabbits. Bourneville and Bricon[10] state that in sporadic cretinism in which the thyroid is lost the pituitary has been found to be enlarged. Boyce and Beadles[11] and other observers found an increase in size of the pituitary gland in hyperthyroidism, while Abram[12] noted changes in this gland in a case of carcinoma of the thyroid. Marie and Marinesco[13] described a case of acromegaly in which there was simple hypertrophy of the thyroid and thyroid-like tissue of the hypophysis. Schöneman[14] in 85 cases of goiter found marked changes in the pituitary in all but one instance.

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[1] The Pituitary Body and its Disorders, p. 10.

[2] Nothnagel's Handbook, 1897, p. 7.

[3] Jokoloff: Virchow's Archives, vol. 13.

[4] Quoted by Cushing: Loc. cit., p. 20.

[5] New York Med. Jour., 1921, 113, 370.

[6] Ibid., 1914, 99, 101.

[7] Modern Medicine (Osler and McCrae), 1915, 4, 803.

[8] Ueber das Verhalten der Hypophysis des Kanninchens nach Entfernung der Schildrüse, Ziegler's Beiträge, vol. 10.

[9] Fortschr. d. Med., 1892, No. 4.

[10] Arch. d. Neurol., 1886.

[11] Bacteriol. and Pathol., 1892, 1, 223 and 359; February, 1893. Pathologic Reports, University College, London, 1892-93, vol. 1.

Conversely, in animals subject to experimental hypophysectomy, definite histological alterations in the thyroid have been observed. For example, Caselli[15] found hypertrophy of the entire thyroid apparatus. The view of Comte[16] and Hoskins[17] that these two glands can function vicariously for one another is supported by the results of total or nearly total extirpation of the hypophysis and those of thyroidectomy.

Of 15 cases of pituitary disease in Cushing's series, in which the thyroid was examined microscopically, all showed "a low epithelium with excess of colloid." It should be noted that at the time of his examinations all of the cases were evidencing signs of glandular insufficiency.

Exner[18] relates that in 2 of Hochenegg's cases of acromegaly, after partial extirpation of the pituitary, enlargement of the thyroid occurred. Says Cushing,[19] "It is my impression that the gland is most liable to show enlargement in individuals with clinical evidences of past hyperpituitarism"—suggesting, in other words, that the same underlying biochemical factor causes a hyperplasia of both structures rather than that the thyroid assumes a compensatory and vicarious role for the hypophysis. Observations upon tumors of the hypophysis were described as early as 1810, when Wenzel[20] tried to link epilepsy with diseases of the pituitary. To Friedreich[21] we owe the first attempt to formulate the symptoms of pituitary new growths.

Cushing[22] has described cases of acromegaly in which with overgrowth and overactivity of the anterior lobe are associated symptoms of posterior lobe insufficiency, *i. e.*, adiposis, increased sugar tolerance, polyuria, polydipsia, subnormal temperature, dry skin, loss of hair, epileptiform disturbances and the like.

Pineles[23] has emphasized the clinical relationship between acromegaly and myxedema, as shown, he believes, by the comparatively frequent coexistence of the two conditions, by the similarity of many of the symptoms and by the occurrence of similar pathological changes in the two conditions. Without doubt these two glands exhibit points of resemblance both from a histological and a physiological viewpoint, so that their commonly observed clinical association should be expected. To show the similarity of their effects upon metabolism it is only necessary to call attention to the fact that myxedema occurring before the growth of the bones is completed causes an arrest of ossification. Functional associations between the pituitary, adrenal, thymus, pineal and genital glands are also recognized, but these will not receive consideration here for want of space.

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[12] Liverpool Med.-Chir. Jour., July, 1896.

[13] Anatomie pathologique de l'Acromegalie, Arch. d. méd. exp., 1891.

[14] Virchow's Archives, 1892.

[15] Riv. sper. di fren., 1900, p. 468.

[16] Beitr. z. path. Anat. u. z. allg. Path., 1898, **23**, 90.

[17] Am. Jour. Med. Sci., 1911, **141**, 374, 535.

[18] Beiträge zur Pathologie und Pathogenese der Akromegalie, Mitt a. d. Grenzgeb. d. Med. u. Chir., 1909, **20**, 620-644.

[19] Loc. cit., pp. 280-281.

[20] Ueber den Hirnanhang fallsuchtiger personen, Mainz, 1810.

[21] Beiträge zur Lehre von den Geschwülsten innerhalb der Schädelhöhle, Wurzburg, 1853.

[22] Am. Jour. Med. Sci., March, 1913, p. 313.

[23] Volkmann's klin. Vortr., 1899, p. 242.

Whether in the cases of associated changes in the pituitary and thyroid the latter shows atrophy or hypertrophy in the majority of the cases is, perhaps, no longer a moot question (*vide infra*). For example, Schönemann[24] believes that an increase of hypophysis may take place in cases of hypertrophy of the thyroid gland; he has, however, "failed to find any compensatory increase of the hypophysis in goiter—that is, in cases of degeneration of the thyroid or in cachexia strumipriva." On the other hand, Souza-Leite,[25] based on an extensive collection of cases, holds that an atrophy of the thyroid is more frequently associated with an enlarged hypophysis than hypertrophy of the thyroid. Hutchinson[26] affirms that the thyroid is atrophied in about 10 per cent of all cases of acromegaly and enlarged in 30 per cent, the enlargement being due usually to cystic degeneration.

It would appear that practically all of the larger earlier post-mortem reports of fatal myxedema in which the hypophysis was examined no abnormalities were observed. We venture to believe, however, that solitary instances of the association of lesions under discussion is decidedly more common than was formerly supposed. Moderate increase in size and microscopical structural changes which are not infrequently present are easily overlooked unless the examinations be thorough and complete.

The effects of hyperactivity of the anterior hypophysis differs in different cases with alterations in the functions of the other internal glands, more particularly the thyroid gland. In this connection the observation of Berkeley[27] that the anterior lobe of the hypophysis is abundantly supplied with sympathetic fibers while the posterior lobe is devoid of such fibers, goes far toward explaining the interrelation between diseases of the former and hyper- and hypothyroidism.

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[24] Quoted by Boyce and Beadles: Loc. cit.

[25] L'Acromegalie, Paris, 1890.

[26] New York Med. Jour., 1898, No. 11, vol. 67.

[27] Quoted by Bell, p. 32.

In a previous paper by us[28] the purpose was, among other things, to collect all cases of pituitary disease recorded in literature covering a period of five years terminating December 31, 1913, and to aid in clearing the question of the relation of hypo- and hyperthyroidism to acromegaly on the one hand and glycosuria on the other. In 5 out of 16 cases (31.5 per cent) of acromegaly in which the thyroid was reported on changes were noted. Of these the thyroid was small in 1, normal in 1, sclerotic and cystic in 1, not palpable in 1, while the remaining case (our own) showed well-marked evidences of hyperthyroidism. These figures would appear to show that the role played by hyperthyroidism in cases of acromegaly is trivial and uncertain. On the other hand they indicate that hypothyroidism is more commonly found in association with pituitary disease.

It is of much interest to note that while acromegaly is regarded as being a rare disease, six years after Marie[29] first described the condition Collins[30] was able to collect about 90 cases from the literature. In 1898 Hinsdale[31] found reports of 130 cases, of which 23 showed exophthalmos, and in the same year Woods Hutchinson collected 218 cases.

In 1893 James J. Putman[32] treated a case of acromegaly with thyroid powder (gr. xv every second day); the condition improved markedly, the enlargement of the hands and feet having practically disappeared. We believe it is safe to infer that in this instance hypothyroidism was associated and that the hypertrophy affected principally the soft tissues. Putman refers briefly to 2 additional cases, "The one stands nearer to acromegaly and the other to myxedema, though in both the diagnosis is doubtful." Both were given thyroids with excellent results. In the former there was a large swelling of the neck, "probably a thyroid, which is diminishing under thyroid extract." There can be but little doubt that this was an instance of combined pituitary and thyroid disease, since hypothyroidism is known to occur in subjects showing enlargement of the gland. Such cases we believe are common examples of advancing hypopituitarism associated with hypothyroidism. They are, as a rule, greatly benefited by careful glandular therapy.

On the other hand Burns's, Benson's and Mosse's cases (quoted by Hinsdale) treated with thyroid extract showed improvement principally in the subjective symptoms, more particularly in the nervous phenomena, without diminution in the size of either the lips, hands or feet. In such an absolute diagnosis of an associated hypothyroidism would be unwarranted. In this connection it is to be borne in mind that in myxedema the hypertrophy affects the

[28] AM. JOUR. MED. SCI., 1914, **147**, 323.
[29] Revue de Méd., 1886.
[30] Jour. Ment. Nerv. and Dis., 1892.
[31] Acromegaly, 1898, p. 23.
[32] Tr. Assn. Am. Phys., 1893, **8**, 338.

soft tissues exclusively, although the basal metabolism, especially as related to the nervous system, is decreased in this disease. Improvement in the mental condition, however, in the absence of a favorable effect upon the soft tissues in myxedema is contrary to universal experience

The growing tendency to regard individual cases of glandular disease as being of pluriglandular origin is unjustified. As pointed out by Falta[33] in speaking of pathological correlation, "The disease that has first involved one gland involves in its further course other members of the ductless glandular system." True it is that upon close analysis of the history, symptoms and course of a given case it is quite frequently possible to discern which ductless gland was first affected.

Secondary to primary involvement of the hypophysis the symptomatic indications of both hypo- and hyperactivity of the thyroid may arise. That the converse may obtain, however, seems to be supported by ample evidence, *e. g.*, in certain cases of Graves's disease. Bell[34] has studied the pituitary in disease of the thyroid. He described the results of a histological examination in a case of cretinism in a female who died at the age of thirty-three years; the structural characteristics found indicated considerable activity, which he thinks were probably compensatory in character.

In exophthalmic goiter many more basophils than is normal are found in the pars anterior, while in the pars posterior the number is normal. Certain it is, however, that reliable deductions must await further information concerning secondary pluriglandular effects. At all events it would seem to us highly probable that the effect upon the pituitary (anterior lobe and intermedia) is more marked after the removal of the thyroid than after the removal of other hormonopoietic organs.

Friedman[35] claims there is a certain degree of hypophyseal hyperactivity in hyperthyroid and of hypoactivity of the pituitary in hypothyroid states. If this be true, then, pituitary products are contraindicated in the treatment of Graves's disease, but indicated in addition to thyroid in myxedematous subjects. This dictum receives confirmation from the histological studies of the hypophysis in hyperthyroidism and myxedema by Fry,[36] who points out that in the former condition the histology corresponds to a gland of high activity and in the latter to a gland of low activity. The pituitary in myxedema is anatomically a hypertrophied gland, but physiologically an atrophied one.

It is especially in these hybrids that mild forms of hypothyroidism, which are so difficult to diagnosticate, are liable to occur; but their recognition is important, as shown by the happy effects of metabolic stimulation by means of thyroid extract so far as the myxedematous manifestations are concerned. As elsewhere stated by one of us:[37] "In both the skin is dry; the subcutaneous fibrous connective tissue is thickened by overgrowth; the tongue is enlarged; the mucous membranes, especially of the nose, soft palate and uvula, are thickened; and menstrual disorders in the female; in both there is irritability of temper, slowness of the mental processes and thick, difficult speech."

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[33] The Ductless Glandular Diseases, second edition, p. 440.

[34] The Pituitary, William Wood & Co., New York, p. 262.

[35] Loc. cit.

[36] Quart. Jour. Med., 1914–15, 3, 277.

Certain obvious features, however, belong to each of these diseases alone when found to be combined. For example, the general bony enlargement with separation of the condyles, spreading apart of the teeth, increased growth of the hair on the head, enlarged joints, the severe headaches and increased muscular strength followed by muscular weakness; in women hairiness assuming the male type, disturbances of vision and bilateral hemianopsia are dependent on the acromegaly; while the tendency to chilling, a subnormal temperature, diminished metabolism, elastic skin—dry and scaly (no pittings)—miniature thyroid, malar flushes, loss of hair, slow small pulse, often arteriosclerosis and slight albuminuria, as well as a peculiarly distorted physiognomy (masked facies), belong to myxedema. Attention should be directed here to those minor forms in which the symptoms are merely suggestive of associated hypothyroidism. In such the cautious use of thyroxin is advised in order to confirm the diagnosis.

In associated hyperthyroidism the cardinal symptoms, such as tachycardia, tremor, exophthalmos, nervousness, increased sweating and increased metabolism, may be more or less frankly expressed, in which case an assured diagnosis is beyond question. In certain cases the degree of hyperthyroidism is moderate or even slight and the symptoms presented are indefinite and variable. Slight tachycardia, a moist delicate skin, a tendency to diarrhea, often polyuria, amenorrhea, slight increase in size of the thyroid, and somewhat widened palpebral fissures and an increased metabolic rate, which is a reliable criterion, are among the most significant diagnostic features in these mild, atypical forms. In the sympathicotonic type one may observe exophthalmos with tachycardia, but no sweats or diarrhea, marked falling out of the hair or alimentary glycosuria.

In this connection Janney's[38] view that the classic symptoms of exophthalmic goiter are of toxic origin or due to a perverted rather than to mere excess of thyroid secretion is to be recollected. If we accept this theory we shall be in a position to appreciate how toxic and hypothyroid symptoms may be combined in a given case. Again, in cases of acromegaly with associated exophthalmic goiter and deficiency symptoms small doses of thyroid extract may prove useful while larger ones would produce an unfavorable effect. Before forming a final diagnostic opinion, however, exophthalmos due to the pressure effects of the hypophyseal enlargement must be eliminated. It is to be recollected that a state of thyroid insufficiency following hypophyseal overactivity is not reached before death in all cases, but only in those in which degenerative changes occur.

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[37] Anders: Diagnosis of Myxedema, AM. JOUR. MED. SCI., 1920, 160, 801.

[38] Arch. Int. Med., August, 1918, p. 187.

An examination of the literature reveals not a few cases of combined pituitary and thyroid disease in which the manifestations of hypothyroidism overshadow those of hypophyseal disease. To overlook the true nature of these is unfortunate in view of the happy effects of appropriate glandular therapy. We have personally observed modifications of the function of the thyroid in two cases of acromegaly, which are here briefly detailed:

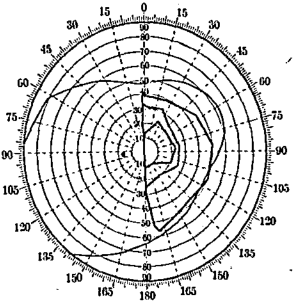
Case I.—A. J. M., female, aged thirty-four years; single; weight, 168 pounds; teacher in the public schools; was referred to one of us for study and treatment by Dr. S. Lewis Ziegler, November 3, 1917. The paternal grandfather died of apoplexy, also the maternal grandfather. The patient had some of the childish diseases and during adolescence repeated attacks of tonsillitis. Eight years ago she was operated on for tuberculosis of the "right tube and ovary"; the wound is still unhealed (fecal fistula). The patient had been taking little exercise and menstruation had always been delayed and scanty, followed by amenorrhea during the past fourteen years. For a long time she had been constipated and complained of nervousness, irritability and was annoyed by any noise; during the past year she had much headache and always felt chilly. During the past two years she noticed a divergence of the left eye, and states that for about eight years she had large bones.

Status Praesens. Bones of face, hands and feet as well as those of the trunk unusually large; hands and feet especially broad in bony parts, spade-like; lower jaw prognathus. Complains of severe headaches at times with nervousness and marked irritability of temper; speech is slow, thick and leathery.

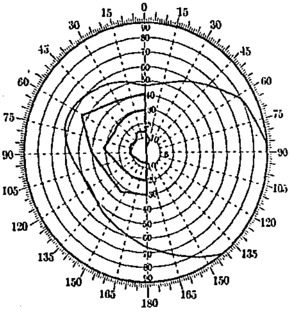
Myxedematous infiltration of the skin of the face and extremities is present, but had not been previously recognized. An associated symptomatic anemia is more marked than usual. For example a blood count showed erythrocytes, 3,110,000; leukocytes, 6000; color index, .9; hemoglobin, 55 per cent. The skin exhibits a slightly yellowish hue with marked pallor of the mucous membranes. The thorax is negative; a fecal fistula is noted in the right lower quadrant of the abdomen. The thyroid is not palpable. The urine proved negative and there is increased sugar tolerance.

Dr. Ziegler reports eye-findings as follows: "She first noticed diplopia about one year ago, which doubtless was caused by the muscular error in her eyes, which amounts to a hyperphoria of 4 degrees and an exophoria varying from P 18 degrees to P 20 degrees. Her refraction is compound hypermetropic astigmatism of low grade. I have corrected the hyperphoria, but cannot correct the exophoria without again causing her diplopia, as one eye wanders off far enough to limit her to monocular vision. The nerve head shows slight pallor on the temporal side. The fields are absolutely hemianopic with some contraction, as is indicated in the charts of the same, which I enclose."

LEFT



RIGHT



A roentgen-ray study by Dr. G. E. Pfahler follows: "I find great thickening of the skull. The cranial vault is approximately 2 cm. in thickness—three or four times as thick as normal. There is a tumor in the region of the pituitary and this tumor has extended both upward above the sella and has broken through the floor of the sella, extending into the region of the sphenoid. This is the first time that I have seen such a condition (in which the tumor has extended through the floor). The clinoid processes are not widely separated or destroyed, as is commonly the case, probably due to the fact that the tumor has extended downward more than upward. The hands show the thickening about the ends of the distal phalanges, and in fact general thickening about the ends of all of the phalanges and of all of the metacarpals. They have the appearance that we commonly find in acromegaly." The case is looked upon as one of acromegaly with associated myxedema and tuberculosis.

The use of thyroid extract in small doses has been remarkably effective for good. Not only has there been a marked subsidence of all of the myxedematous features, but the headaches, speech and nervous irritability have also been greatly relieved. The bony skeleton, however, has remained stationary.

CASE II.—A. H., aged forty-six years, female, occupation cook, weight 170 pounds, height 5 feet 9½ inches, first came under the care of our surgical colleague, Dr. William L. Rodman, in the Medico-Chirurgical Hospital, December 5, 1913, at which time she was suffering from a gangrenous wound, inflicted by a fish-bone, of the left hand. A few days later the patient was referred to the medical service (to us) for study and treatment. Polydipsia, polyuria and glycosuria, as well as bulimia, were all prominent features throughout the illness. The percentage of sugar at first was 5 per cent, but at the end of one week it rose gradually to 7 per cent, and remained at this level until the end.

The typical symptoms of acromegaly were in evidence. According to the history the bones of the hands and face began to enlarge four years ago while the glycosuria set in about two years later. A roentgen-ray examination by Dr. Pfahler showed marked lipping at the edges of the articular surfaces of the metacarpal bones and phalanges, such as is found in acromegaly, and also a tumor of the pituitary gland, with absorption of the clinoid processes. The diagnosis of associated hyperthyroidism was quite apparent from the noticeable enlargement of the thyroid gland, together with tremor, tachycardia and exophthalmos. The indications of exophthalmic goiter were most probably developed after the glycosuria had existed for an indefinite period of time, although being, as is usual, of insidious origin, it was impossible to fix the precise date of onset. The Wassermann reaction gave a negative result.[39]

With a view of indicating the true pathological relationship between disease of the hypophysis and thyroid the results of a statistical study are subjoined. The total number of cases collected by us, which was 215, includes only a few that were reported prior to the publication of the paper of Dr. Hinsdale in 1898 and that of Hutchinson in 1902. Table I is a detailed tabulation of 91 cases in which thyroid disturbance was associated.

It should be pointed out that the notations to be found in the columns headed hyper- and hypothyroidism are the inferences drawn by the original reporters, with few exceptions. Failure to record the sugar tolerance and condition of the thyroid gland and its function in numerous cases is to be regretted. It is interesting to note that all of our series, or 215 cases, occurred in the white race with a single exception, which was reported by Yamada, of Tokio (*vide* Table I). Trauma played a role in 3 cases and in 2 the disease followed "psychic trauma." According to these findings the influence of traumatism as a disposing factor is insignificant. There can be no doubt but that a family type exists, although the influence of heredity must, on the whole, be trivial, as evidenced by our results, namely, two instances only of the entire series.

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[39] This case is more fully reported in a previous article by Anders and Jameson, loc. cit.

TABLE I

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Lancereaux	Semaine méd., 1895, xv, 61	40	F	Hypertrophy	Present	....	....	Present	Trauma.
Henrot	Quoted by Lancereaux, loc. cit.	36	M	Goiter	Present	....	Tumor size of hen's egg	Present	Reported in 1877; heart hypertrophied.
Valat	Idem.	..	..	Goiter	Present	....	....	.....	Reported in 1893.
Haskovec	Wien. klin. Rundschau, 1895, ix, 257	35	M	Atrophy	....	....	....	Absent	Head injury followed by meningitis.
Sears	Boston Med. and Surg. Jour., 1896, cxxxv, 16	45	F	....	....	Present	....	Absent	Improved by thyroid administration.
Dodgson	British Med. Jour., 1896, i, 660	23	F	Enlarged					
Worcester	Boston Med. and Surg. Jour., 1896, cxxxiv, 413	70	F	Not palpable	....	Marked	Sarcoma with psammomatous degeneration	.....	Myxedema disappeared under thyroid treatment.
Furnival	Lancet, London, 1897, ii, 1190	58	M	Slightly enlarged and altered in function	....	....	Adenoma-cystic degeneration		
Dalton	Idem.	..	..	Normal, except thyroid juice unusually fluid	....	Present	Sarcoma or hypertrophy and posterior lobe almost disappeared	Present	Thymus normal.
Murray	Edinburgh Med. Jour., 1897, i, 170	37	F	Goiter	Present	....	....	Present	Pulmonary tuberculosis.
Murray	Idem.	63	F	Large cystic goiter	Absent	....	....	Absent	
Murray	Idem.	34	F	Enlarged	Present	....	Enlarged	Present	Pulmonary tuberculosis; thymus hypertrophied.
Schiff	Wien. klin. Wchnschr., 1897, x, 277	37	M	....	....	Present	....	Increased tolerance	

Schiff	Ztschr. f. klin. Med., 1897, xxxii, 289, Suppl.	..	..	....	....	Present	....	....	Unable to consult article
Osborne	Tr. Assn. Am. Phys., 1897, xii, 262	47	M	Enlarged 101 gm., extrathyroid in chest, 36½ gm.	....	....	Sarcoma (?)	.....	Heart enormous.
Comte	Beitr. z. path. Anat. u. z. allg. Path., 1898, xxiii, 90	46	F	Much enlarged	Present	....	Enlarged 0.415 gm.		
Comte	Idem.	32	F	Enlarged 390 gm.	Present	Absent	Enlarged 0.85 gm.		
Bailey	Philadelphia Med. Jour., 1898, i, 789	65	F	Parenchymatous hypertrophy; nearly 3 times normal weight	....	....	Adenoma		
Hunter	Tr. Path. Soc., London, 1898, xlix, 246	52	M	Hypertrophy	....	....	Hypertrophy		
Neal	Ibid., p. 237	41	F	Parenchymatous goiter 6½ oz.	Absent	....	Hypertrophy	.....	Slight improvement under thyroid.
Coe	Jour. Am. Med. Assn., 1898, xxxi, 1347	68	F	Small	....	....	....	Absent	Homicidal.
Thompson	Med. Press and Circ., London, 1898, n. s., lxv, 377	19	F	....	....	Present	....	Absent	
Ponfick	Ztschr. f. klin. Med., 1899, vol. i.	47	M	Marked atrophy	....	Present	Chronic interstitial inflammation and atrophy		
Lediard	British Med. Jour., 1903, i, 789	43	F	Bilateral goiter (large)	....	....	....	Previous glycosuria	Left lobe removed with improvement in pressure symptoms.
Cattle	Ibid., p. 780	30	F	Goiter	Present	....	....	Absent	Exophthalmos, tachycardia and excessive sweating.
Snell	Ibid., ii, 131	38	F	Not enlarged	....	Present	....	Absent	Improved under thyroid treatment.
Launois and Roy	Nouv. iconog. de la Salpêtrière, Paris, 1903, xvi, 163	36	M	Hypertrophy; 250 gm.	....	....	Large epithelioma	Present	

TABLE I.—(*Continued.*)

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Heising	Wisconsin Med. Jour., 1903–04, ii, 684	38	F	Small	....	....	....	.....	Preceded by severe psychic trauma; thymus persistent.
Bate	Louisville Month. Jour. Med. and Surg., 1903–04, x, 374	28	F	....	Probable		....	.....	Attributes tachycardia (100) to overaction of thyroid-like tissue in pituitary.
Salomon	Berl. klin. Wchnschr., 1904, xli, 635	49	M	....	Probable	....	....	.....	Increased metabolism; skin resembles myxedema.
Salomon	Idem.	42	M	....	Present	....	....	.....	Increased metabolism; skin resembles myxedema; marked arteriosclerosis.
Greene	New York Med. Jour., October, 1905, p. 846	25	M	Small	....	Present	....	Absent	Myxedema disappeared under treatment.
King	South. California Pract., 1905, xx, 410	37	M	....	Absent	Previous myxedema	....	Absent	
Kerry	Ophth. Rev., London, 1905, xxiv, 193	50	M	....	....	Probable	....	.....	Marked improvement under thyroid treatment.
Ballet and Laignel Lavastine	Nouv. iconog. de la Salpêtrière, Paris, 1905, xviii, 176	70	F	Hyperplasia	....	....	Parenchymatous hypertrophy	.....	Hyperplasia of adrenals
Taylor	W. London Med. Jour., 1905, x, 124	34	F	....	....	Probable	....	.....	Sent as case of myxedema.
Schoenborn	Beitr. z. path. Anat. u. z. allg. Path., 1905, Suppl., vii, 468	65	M	Cystic goiter with interstitial inflammation	....	.....	Adenoma size of walnut	Absent	Cardiorenal asthma.
Porter	Ophth. Rec., Chicago, 1906, xv, 267	47	F	Greatly enlarged	Present				

Curren	Maritime Med. News, Halifax, 1907, xix, 98	20	F	"Thickening in region of thyroid"	Present				
Haywood	Homeopathic Eye Jour., 1907, xiii, 48	33	F	....	Present	....	....	.....	Improved by pituitary treatment; atrophy of ovaries and uterus.
Sainton and Rathery	Soc. méd. d. hôp., Paris, 1908, xxv, 647	32	F	Atrophy and sclerosis	....	Present	Malignant tumor	Absent	Thymus persistent.
Renon and Delille	Ibid., p. 973	47	F	....	....	Present	Tumor	Absent	
Kocher	Deutsch. Ztschr. f. Chir., Leipsig, 1909, c, 13	30	F	Small	....	....	Sarcoma	Present	Thymus persistent; operation.
Carmody	Lancet, London, 1909, i, 1599	33	F	Previous goiter	....	....	....	Absent	Skin thick but could be pinched, now abnormally active; no improvement under pituitary treatment.
Exner	Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, xx, 620	30	F	Enlarged after operation on pituitary	....	....	Malignant adenoma	Tolerance increased	Tongue, lips, hands and feet smaller after operation.
Exner	Idem.	34	F	Isthmus became size of walnut after operation	....	....	Malignant adenoma	Tolerance increased	
Packard	Am. Med., 1910, n. s., v, 539	36	F	Hypertrophy	....	....	*X*-ray unable to demonstrate tumor		
Grove	Bull. Johns Hopkins Hosp., 1910, xxi, 290	47	F	Colloid goiter	....	Present	Enlarged	Absent	Partial thyroidectomy.
East	Jour. Mental Sci., 1912, lviii, 631	43	F	Enlarged	....	....	....	.....	Mental symptoms.
Cushing	Pituitary Body and its Disorders, Philadelphia, 1912, p. 30	35	M	Small	Absent	Absent	Adenoma	.....	Ac. secondary to gigantism; exophthalmos due to neighborhood pressure.
Cushing	Ibid., p. 36	26	F	Colloid goiter	Absent	Absent	Adenoma		
Cushing	Ibid., p. 85	36	M	Large and colloidal	Absent	Absent	Tumor	.....	Slight acromegaly followed by hypopituitarism: trauma.

TABLE I.—(*Continued.*)

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Cushing	Ibid., p. 137	40	M	Slightly enlarged	Absent	Absent	Slight enlargement of sella turcica	.....	Hypertrichosis.
Cushing	Ibid., p. 140	38	M	Colloid goiter	Absent	Absent	Chromophil-struma		
Cushing	Ibid., p. 150	59	M	"Plunging goiter"	Former	Absent	Enlarged	.....	Goiter removed.
Cushing	Ibid., p. 154	42	M	"Possibly enlarged"	Absent	Probable	....	.....	Benefited by thyroid treatment; complicated by gigantism, hay fever and tuberculous adenitis.
Cushing	Ibid., p. 194	33	M	Enlarged; excess of colloid	Absent	Absent	"Functional hyperplastic change"	.....	Secondary to hydrocephalus.
Holmes	Proc. Roy. Soc. Med., London, 1912–13, vol. vi, Neurol. Ophth. Sect., X	36	F	....	....	Probable	Sella turcica enlarged	.....	Improved under thyroid treatment.
Garrod	Ibid., lxxviii	..	..	....	....	Present	Sella turcica enlarged	.....	Improved under thyroid.
Brown	Ibid., lxxxvii	40	F	Cystic goiter	....	"Possible myxedema"	....	Tolerance increased	Previous acromegaly, now hypopituitarism; some improvement under thyroid.
Bartlett	Tr. Chicago Path. Soc., 1913, ix, 56	25	M	Colloid goiter	....	....	Chromophil-cell adenoma	.....	Thymus persistent.
Gordinier and Kirk	Albany Med. Ann., 1913, xxxiv, 189	39	F	Distinctly enlarged	....	....	Tumor		
Grinker	Jour. Am. Med. Assn., 1913, lxi, 235	49	M	Absent	....	Present	Large adenoma	Intermittent	Followed infected vaccination and psychic trauma; benefited by thyroid; epilepsy.

Millioni	Riforma med., Naples, 1913, Nos. 39, 40 and 41, vol. xxix	34	F	Small	....	Present	Marked enlargement; probably tumor	Absent	
Fernsides	Proc. Roy. Soc. Med., London, 1913-14, vii; Electro-therap. Sect., 46	40	F	Not palpable	....	Present			
Dunn	Am. Jour. Med. Sci., 1914, cxlviii, 214	61	M	Small	....	....	....	Tolerance increased	Hemoptysis; non-tuberculous; angioneurotic edema.
Anders and Jameson	Ibid., p. 323	46	F	Goiter	Present	....	Tumor	Present	Gangrene.
Osborne	Proc. Connecticut State Med. Soc., 1914, p. 164	40	M	....	....	Present			
Chizet	Lyon méd., 1914, cxxii, 882	15½	M	....	....	Present	Tumor	.....	Polyuria.
Bendell	Albany Med. Ann., 1915, xxxvi, 441	45	F	Colloid enlargement					
Fürth	Med. klin. Berl., 1915, xi, 1347	40	F	Palpation negative	....	Deficient iodine production	Tumor	.....	Temporary improvement under iodide treatment, father had goiter.
Falta	Ductless Glandular Diseases, Philadelphia, 1916, p. 237	32	M	Enlarged	....	....	....	Tolerance increased	Heart enlarged; hypertrichosis.
Falta	Ibid., p. 243	31	M	Slightly enlarged	....	....	....	Tolerance increased	Hypertrichosis.
Falta	Ibid., p. 243	31	M	Not enlarged	Probable	.....	Adenoma	.....	Hypertrichosis; thyroid in aggravated symptoms; temporary improvement after operation.
Falta	Ibid., p. 246	33	F	Enlarged	....	....	....	Tolerance decreased	Marked hypertrichosis; lues.
Falta	Ibid., p. 253	37	F	....	Present	....	Grayish-red tumor	Tolerance decreased	
Falta	Ibid., p. 266	31	F	....	Present	Present	....	Tolerance decreased	Hyper- followed by hypothyroidism.

TABLE I.—(*Continued.*)

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Futcher	Med. Clin. North America, 1917, i, 131	67	F	....	Absent	Possible association of myxedema	Sella turcica enlarged	Tolerance increased	Possible early paralysis agitans.
Soner	Med. Jour. So. Africa, 1918, xiii, 102	34	F	....	Absent	Present	....	.....	Improved under thyroid treatment.
Yamada	Mitt. a. d. Med. Fac. d. k. Univ. z. Tokyo, 1918, viii, 411	17	M	Hypertrophy	....	....	....	.....	Thymus persistent; died of beri-beri.
Good and Ellis	Endocrinology, 1918, ii, 431	58	M	Atrophy	....	Present	Hemangio-endothelioma	Tolerance increased	Thymus persistent; testes and adrenals atrophied and sclerotic.
Lewis	Laryngoscope, 1918, xxviii, 604	34	F	....	....	Present			
Loewenberg	Internat. Clinics, 1918, 28th ser., iii, 154	34	M	Slightly enlarged	....	....	Tumor (calcified)	.....	Pulmonary tuberculosis.
Roth	Berl. klin. Wchnschr., 1918, lv, 305	28	M	Enlarged	....	....	Tumor	Absent	Developed copious milk secretion.
Howard	Am. Jour. Med. Sc., 1919, clviii, 830	31	M	Slight cystic degeneration	....	Probable	Round-cell sarcoma	Tolerance increased	
Howard	Idem.	47	F	Slight goiter	Probable	....	....	Present	
Webster	Arch. Radiol. and Electro., London, 1919–20, xxiv, 261	..	..	Enlarged	....	....	....	Tolerance increased	Headaches relieved by *x*-ray.
Tierney	Med. Clin. North America, 1920, No. 3, iv, 799	40	M	Enlarged	....	....	....	Tolerance increased	Father and sister acromegalic types.
Barr	New York Med. Jour., 1920, cxi, 248	36	M	Enlarged	....	....	Sarcoma	.....	Imbecile.
Bernstein	Not published	39	M	Small	....	Probable	Large adenoma	Tolerance increased	Operation relieved headache, preserved vision; acromegaly stationary since.
Anders and Jameson	Not previously published	34	F	Small	....	Present	Tumor	Tolerance increased	Improved by thyroid treatment.

TABLE II.—TOTAL CASES OF ACROMEGALY, 215

Age (cases mentioned, 195).		Sex (cases mentioned, 194).		Lesions of pituitary (cases mentioned, 99).		Lesions of thyroid (cases mentioned, 68).		Glycosuria (cases mentioned, 91).	
Male.	Female.	Males.	Females.					Present.	Absent.
37.14	38.76	90 (46.4 per cent)	104 (53.6 per cent)	"Tumor"	41	Enlarged	24	32 (35.2 per cent)	59 (64.8 per cent)
				Adenoma	15	Goiter	20		
Average age, 38.3				Sarcoma	12	Atrophy	17		
				Sella turcica enlarged	13	Hypertrophy	7		
				Enlarged	6	Functional	23		
				Hypertrophy	3				
				Various	9				

TABLE III.—COMBINED ACROMEGALY AND THYROID DISTURBANCE, 91 CASES

Age (cases mentioned, 86).		Sex (cases mentioned, 86).		Lesions of pituitary (cases mentioned, 47).		Lesions of thyroid (cases mentioned, 68).		Glycosuria (cases mentioned, 47).	
Male.	Female.	Males.	Females.					Present.	Absent.
39.64	39.98	37 (43 per cent)	49 (57 per cent)	"Tumor"	13	Enlarged	24	14 (30 per cent)	33 (70 per cent)
				Adenoma	11	Goiter	20		
				Sarcoma	6	Atrophy	17		
Average age, 39.85				Enlarged	4	Hypertrophy	7		
				Sella turcica enlarged	4	Functional	23		
				Hypertrophy	3				
				Various	6				

TABLE IV.—ACROMEGALY WITHOUT THYROID DISTURBANCE, 124 CASES

Age (cases mentioned, 109).		Sex (cases mentioned, 108).		Lesions of pituitary (cases mentioned, 52).	Glycosuria (cases mentioned, 44).	
Male.	Female.	Males.	Females.		Present.	Absent.
35.4	37.67	53 (49 per cent)	55 (51 per cent)	"Tumor" . . . . 28 Sella turcica enlarged . . 9 Sarcoma . . . . 6 Adenoma . . . . 4 Cyst . . . . 2 Enlarged . . . . 2 Degeneration 1	18 (41 per cent)	26 (59 per cent)
Average age, 37.18						

A review of Table II shows that in 99 cases out of the 215 cases of acromegaly the lesions of the pituitary are mentioned and that in 68 cases thyroid changes are recorded. It is noteworthy that only three more examples of adenomata than sarcomata are reported among the pituitary lesions, it being currently stated by the older as well as recent writers that the great majority of the new growths of this gland in acromegaly are adenomata. The influence of sex upon the incidence of the disease is shown by a slight preponderance in favor of the female. On the other hand Hinsdale's figures indicate that the disease is more common in the male than in the female sex; for example, he found 73 males and 57 females in his series of 130 cases. The average age here given (thirty-eight and three-tenth years), which represents that of the ages reached at the time the cases were reported, is too high, but the date of onset was so frequently indeterminable from the histories recorded in the literature as to make this course necessary. Table III needs no description.

Table IV shows the age incidence to be slightly higher in the combined pituitary and thyroid cases than in the uncombined acromegalics and also a slightly greater preponderance in the female as compared with the male sex by comparison with acromegaly without associated thyroid lesions. It cannot be stated, however, that these figures afford a basis for the claim often advanced that the thyroid is a true sex gland, as is shown by both Graves's disease and myxedema when they occur independently of the acromegaly. For example, both the latter conditions are six to eight times as frequent in the female as in the male. It will be noted that the proportion of cases of adenoma in Table IV as compared with sarcoma is almost three times greater than in Table III, although the figures are too small on which to base any inferences.

TABLE V.—AGE BY DECADES

Acromegaly without thyroid disturbance.		Acromegaly with thyroid disturbance.	
Under 20 years	3	Under 20 years	3
21 to 30 "	32	21 to 30 "	7
31 to 40 "	34	31 to 40 "	39
41 to 50 "	17	41 to 50 "	25
51 to 60 "	18	51 to 60 "	4
61 to 70 "	4	61 to 70 "	6
71 to 80 "	1	71 to 80 "	2

An inspection of Table V, which presents the age incidence by decades, will show that for acromegaly with associated thyroid disturbance this is considerably higher than in the cases without involvement of the thyroid—an interesting fact. The explanation is probably to be found in the accepted view that thyroid complaints, myxedema in particular, develop later in life than uncomplicated acromegaly, as a rule. This table indicates clearly that the great majority of cases of acromegaly with thyroid disturbance arise between the thirtieth and fiftieth years of age, and that both during the decade prior to that period of life and subsequently the cases are far less numerous than in acromegaly without thyroid disturbance. Again, it should be noted that in the cases of acromegaly in which thyroid disturbance is combined the latter usually arises a number of years after the onset of the former, *i. e.*, when the stage of hypopituitarism is reached.

TABLE VI.—THYROID FUNCTION, 52 CASES

Hyperthyroidism, 20 (38.5 per cent.)		Hyperthyroidism, 32 (61.5 per cent.)	
Male	5	Male	12
Female	14	Female	18
Glycosuria.		Glycosuria.	
Present	7	Present	2
Absent or increased tolerance	1	Absent or increased tolerance	16

Table VI exhibits the facts bearing on the relative incidence of hyper- and hypothyroidism and on the carbohydrate tolerance as well as the influence of sex on the thyroid function. It will be seen that in the hyperthyroid group the ratio in favor of the female is about 3 to 1 while in the hypothyroid cases it is 3 to 2. Again, the incidence of hypothyroidism as compared with that of hyperthyroidism is about as 3 to 2. With regard to the question of carbohydrate tolerance in cases of combined acromegaly and disturbed thyroid function Table VI demonstrates that in hyperthyroidism the sugar tolerance was decreased in 7 out of 8 cases—ratio 7 to 1. On the other hand in the cases of associated hypothyroidism sugar was absent or tolerance increased in the ratio of 8 to 1. It should be added that of the 16 cases belonging to the latter group in 7 the increased sugar tolerance was determined by the usual tests.

Summary. Our literary studies have revealed an unexpected frequency of associated disturbance of the thyroid function in cases of acromegaly, or 33 per cent, as shown by Table I. It is highly probable that in many instances of pituitary disease with its usual syndrome the coexistence of thyroid alterations and symptoms resulting therefrom were overlooked, as was true of one of the two cases which was reported by us. Our investigations indicate that hypothyroidism is more commonly associated with acromegaly than hyperthyroidism, and that those combined cases which manifest myxedematous features are decidedly improved as the result of the use of thyroid preparations.

It follows that the recognition of the indications of hypothyroidism in connection with acromegaly is a matter of the utmost importance. In cases of acromegaly in which merely suspicious features of either hypo- or hyperthyroidism exist it is strongly urged that the metabolic rate be determined. The approved sugar tolerance test should be carried out in all cases of acromegaly with a view of determining the state of both the pituitary and the thyroid function. Nothing of special significance bearing upon the etiological factors of the disease under consideration resulted from our studies, with the possible exception of the facts developed in connection with the age groups by decades (*vide* Table V). Our grateful acknowledgements are made to Dr. Andrew A. Anders for valuable assistance in the literary investigations.

EPILEPTOID OR FAINTING ATTACKS IN HYPOPITUITISM.[1]

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We shall make no attempt to analyze hypophyseal dysfunctions in their relationship to epileptiform seizures. This has been fairly well done by Cushing, Johnston and others. Nor shall we discuss the reverse influence, as that of clinical epilepsy, upon the hypophysis, as in the studies of Munson at Craig Colony, or take time and space to consider the subjects of syncope and fainting in general. Even so simple a clinical observation as that of fainting probably has a very complicated and varied psychical and somatic mechanism. We do wish, however, to call attention to the fact that there is an increasing accumulation of clinical data of apparently idiopathic attacks of fainting without general somatic defect of the viscera. During the past few years several such cases have been referred to me on the suspicion that these individuals were suffering from a larval form of petit mal epilepsy.

We may enumerate briefly some of the salient differences between this special type of syncope and petit mal epilepsy. We must first note, however, that it is commonly stated that individuals who have their first attacks of petit mal are only suffering from a form of fainting dependent upon some dysfunctions of the viscera, a weak heart or indigestion. In other words, both laity and physicians are much more likely to believe that the early attacks of petit mal are but a form of syncope and in consequence of little moment.

As for real differential diagnosis: If there be no obvious or immediate exciting cause such as emotional stress or physical shock the individual attack of loss of consciousness is more likely to be nothing more than a syncopal one. Slow and incomplete loss of consciousness also is in favor of the state being simply that of fainting. While a sensation of faintness is common to both, usually it takes on much more elaborate characters such as are seen in the epigastric aura. This aura has the sensation of a rising of an inde-

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[1] Read before the American Psychopathological Association, June, 1921.